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Complement Inhibition with the C5 Blocker LFG316 in Severe COVID-19

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Author contributions: JC, MPW, BES, CF, MM and MJP identified patients, organised treatment and collected and analysed all patient data. WMZ, MJP, SJ and BPM conducted and/or reviewed all laboratory data. RAH and NW proposed the study and facilitated drug supply for compassionate use. MPW and BPM supervised and coordinated the research and wrote initial manuscript drafts. All authors contributed to revisions, approved the final manuscript and accept accountability for all aspects of the work.

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Conflict of interest: CF has obtained honoraria from Roche, AbbVie, Astra Zeneca and Janssen. RAH is a former employee of Novartis and retains a consulting role. NW is an employee of Novartis. SJ has received support from CSL Behring, Takeda, Shire, Octapharma, Pharming, Biotest, SOBI, LFB, Grifols, BPL, Sanofi, GSK, UCB Pharma, The Binding Site, Weatherden and Zarodex for projects, meetings, advisory boards, DSMB and clinical trials. BPM is a consultant for RaPharma and has provided advice to Alexion, Roche and Janssen. All other authors have no relevant conflicts to declare.

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To the Editor:

In critically ill COVID-19 patients, a hyper-inflammatory host response contributes to organ dysfunction and death. The role of complement in these events is unclear. Complement activation yields powerful pro-inflammatory effectors, notably C5a and membrane attack complex, and triggers coagulation (1); it has been implicated in bacterial sepsis and septic shock, sepsis-like syndromes associated with coronavirus infections, and COVID-19-associated microvascular injury and thrombosis (2-4). Recently, the C5a/C5aR1 axis was implicated in COVID-19 lung pathology (5). We here report the contribution of complement activation and impact of complement blockade in severe COVID-19, defined as marked respiratory impairment requiring intensive care and ventilation support. Drugs were administered under the Managed Access Program and permission to undertake this case series study was granted by the Director of Research and Development at Cardiff and Vale University Health Board.

Complement dysregulation was identified in critically ill, RT-PCR-confirmed COVID-19 patients; terminal complement complex (TCC) and C5a levels were measured in mechanically ventilated patients on the Critical Care Unit at a single centre if the clinician considered that the clinical trajectory was not improving (Figure 1A). Five patients were selected, based on high levels of TCC (above the mean +2sd for controls; 7.14mg/L) and either treatment failure (Patients 1-3) or failure to improve (Patients 4 and 5) where death was not considered imminent (clinical judgement), for inclusion in a compassionate use study of complement blockade using LFG316 (tesidolumab; Novartis Managed Access Programme), a C5-blocking monoclonal antibody (mAb) that prevents generation of the pro-inflammatory effectors C5a and membrane attack complex (6). As patients were unable to

provide written informed consent, assent from relatives was obtained. Pre-treatment disease course is summarised in Table 1. All five patients selected were paralysed and prone whilst receiving mechanical ventilation. HFOV and Nitric oxide (NO) were used alone or in combination in the first three patients. Duration of ventilation prior to LFG316 is shown in Table 1. Each patient received a single 1500mg dose of LFG316 by intravenous infusion, anticipated from unpublished Novartis data to fully inhibit C5 for >7 days, preceded by chlorpheniramine (4mg) and hydrocortisone (100mg). Antibiotic prophylaxis (phenoxymethylpenicillin or clarithromycin) was provided to mitigate risk of encapsulated bacterial infections. In all patients, CH50 was completely suppressed up to day 4 post-treatment with partial recovery at day 7; TCC and C5a levels fell to within the normal range and remained low through day 7; CRP levels were elevated pre-dose and, except for patient 5, fell post-drug (~80%) and remained reduced through day 7 (Table 1). Patients 1,2 and 4 showed rapid resolution of CRP, improved oxygenation and CO₂; recovery in patient 3 was much slower but all showed improved ventilation post-drug (Figure 1B). Patient 5 failed to respond to LFG316 despite complete complement blockade, developed a sudden pulseless electrical activity cardiac arrest and died 9 days after treatment; uniquely, CRP levels did not fall post-treatment in this patient, suggesting that there was another driver of inflammation, likely the identified occult *Klebsiella* infection. Among our severe COVID-19 cohort who did not receive LFG316, 67 of 71 were mechanically ventilated and paralysed, and 28 of these were prone. Mean duration of ventilation in this subgroup was 19.5 days. Death occurred in 13 (46.4%).

Currently there are no proven effective therapies for critically ill COVID-19 patients requiring mechanical ventilation (7). The potential efficacy of anti-complement drug therapy in COVID-19 has been tested in a handful of patients to date and was recently reviewed (8). Diurno *et*

al treated four COVID-19 patients with the C5 blocking mAb eculizumab, weekly x4 (9). All were self-ventilating with moderately elevated CRP that fell after treatment; all recovered over 14 days. Mastaglio *et al* treated a single non-ventilated patient with the C3 blocker AMY-101 continuously infused over 14 days with favourable outcome (10). In each of these reports, patients selected had relatively mild disease and no measurements of complement parameters to assess dysregulation before or in response to drug were reported.

We describe a preliminary evaluation of the potential benefit of C5 blockade in severe COVID-19; we show that the C5 blocking mAb LFG316 could be administered in critically ill mechanically ventilated COVID-19 patients; a single dose of LFG316 blocked C5 activity and complement activation for at least 4 days in all treated patients. In four of five patients, there was sustained improvement in clinical state persisting beyond C5 blockade. An occult *Klebsiella* infection was found in the non-responding patient 5 four days post-drug; given the known impact of complement blockade on risk of infection with gram-negative bacteria, it is possible that LFG316 treatment exacerbated the infection. No other adverse effects of therapy were seen in any of the treated patients. Our results suggest that transient blockade of C5 is sufficient to interrupt the hyper-inflammatory cycle in severe COVID-19 and permit recovery even in the most extreme clinical situations. This finding differs from previous case reports of complement inhibition in COVID-19 where patients were less severely ill and treated for extended periods (8-10). Our data are supportive of ongoing clinical trials of C5 blockade in severe COVID-19 and may inform design of current and future trials of anti-complement drugs where repeated or prolonged complement blockade are proposed; indeed, prolonged complement blockade may not only be unnecessary for patient benefit but may be harmful by increasing infection risk, a known consequence of complement blockade,

over weeks or months in recovering patients, likely on other immune suppressants and with residual lung damage.

Study limitations include small cohort size and lack of a randomised control group. Although our data identify complement dysregulation and support clinical benefit of complement blockade in severe COVID-19, these limitations make it impossible to demonstrate proof-of-efficacy. Further studies are warranted to confirm impact of complement blockade on hyper-inflammatory and/or thrombotic components of COVID-19 disease and to establish optimal timing and dosing.

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Figure 1. Complement activation in severe COVID-19 and response to C5 blockade.

A. Levels of terminal complement complex (TCC; in house ELISA), C5a (Hycult ELISA) and C5 (in house ELISA) were measured in EDTA plasma from severe COVID-19 patients and controls; TCC levels were significantly elevated compared to the healthy EDTA plasma controls (COVID-19, n=25, mean=12.5mg/L; controls n=67, mean=4.1mg/L; $p<0.0001$, unpaired t-test). C5a levels were also significantly elevated compared to healthy controls (COVID-19, n=25, mean 43.0 μ g/L; controls, n=32, mean=14.7 μ g/L; $p<0.0001$, unpaired T test). C5 levels were not different between COVID-19 (n=25; mean=84.5g/L) and controls (n=31, mean=81.8g/L; $p=0.42$). Error bars are standard error in each panel. Control samples were from a healthy adult donor EDTA plasma set that had previously been collected in the laboratory.

B. Serial trends in PaO₂:FiO₂ ratio and PaCO₂ were measured following LFG316 treatment. Plots represent the means \pm 1 standard deviation from arterial blood gas measures taken on the specified day from each of the five patients (labelled below) administered LFG316. Filled squares are PaO₂:FiO₂ ratios, open circles are PaCO₂ levels. Dotted lines indicate grading of Acute Respiratory Distress syndrome (mild: 200-300mmHg; Moderate: 100-200mmHg; or Severe: <100mmHg); grey zone represents normal range for PaCO₂. Rapid clinical improvement in patient 4 leading to extubation on day 3 post-drug obviated the requirement for additional measures.

Demographics		Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
		Male 56 years			Female 40 years			Male 46 years			Female 51 years			Male 74 years		
Past medical history:		Oesophagitis, psoriasis, allergic rhinitis and hypogonadism			Type 2 diabetes, depression, post-traumatic stress disorder, morbid obesity			Lambert Eaton syndrome, glaucoma, type 2 diabetes, penile carcinoma in situ,			Asthma			Hypertension; awaiting surgery for a benign posterior fossa tumour (on dexamethasone)		
Pre-hospital symptomatic period:		8 days			5 days.			10 days			7 days			9 days		
Time from hospital admission to LFG316 admin		34 days			7 days			22 days			12 days			11 days		
Inpatient course, pre-LFG316		4 days of mechanical ventilation on ICU early in COVID course before ward discharge for 14 days, then. ICU readmission.			Rapid escalation to critical care within 48 hours of hospital admission.			Rapid escalation to critical care within 12 hours of hospital admission.			Admitted to critical care day 3 after hospital admission with severe respiratory failure.			Admission to critical care 1 day after hospital admission with severe hypoxia.		
ICU course:	<i>Pre-drug Steroids†</i>	3.75g			0.3g			0			0.45g			0.48g		
	<i>Ventilation duration pre-LFG316</i>	4 plus 12 days			5 days			22 days			9 days			11 days		
	<i>High frequency oscillatory ventilation</i>	No			Yes			Yes			No			No		
	<i>Nitric oxide</i>	Yes			Yes			No			No			No		
	<i>ECMO referral</i>	No			Yes			No			No			No		
	<i>Prone</i>	Yes			Yes			Yes			Yes			Yes		
	<i>Paralysis</i>	Yes			Yes			Yes			Yes			Yes		
	<i>Pulmonary emboli</i>	Yes			No			No			No			Yes		
	<i>Normal range/units</i>	Pre-drug	First 48 ⁰	Day 7-10	Pre-drug	First 48 ⁰	Day 7-10	Pre-drug	First 48 ⁰	Day 7-10	Pre-drug	First 48 ⁰	Day 7-10	Pre-drug	First 48 ⁰	Day 5-8
Haemoglobin	130 - 180 g/L	90.0	92.0	90.0	90.0	102	96.0	90.0	78.0	73.0	93.0	91.0	113	114	116	98.0
Platelets	150 – 400 x10 ⁹ /L	305	342	371	99	480	428	99	75	35	241	227	358	339	324	393
Neutrophils	1.7-7.5 x10 ⁹ /L	7.5	8.2	10.4	17.4	26.2	10.5	17.4	9.9	4.6	5.2	6.3	3.5	7.5	7.3	8.0
Lymphocytes	1.0-4.5 x10 ⁹ /L	1.5	1.1	1.6	0.9	3.0	1.4	0.9	0.4	0.1	1.0	1.2	1.7	1.3	1.0	1.9
Prothrombin Time	9.0- 13.0 seconds	13.0	11.7	-	12.3	13.0	13.0	11.4	-	12.1	12.9	12.6	-	13.0	12.5	13.5
Activated partial thromboplastin time	23.0-38.0 seconds	37.8	39.2	-	28.6	30.9	34.2	33.5	-	29.2	29.3	32.0	-	30.9	33.0	34.5
Fibrinogen	2.0-4.0 g/L	6.3	6.0	-	8.5	6.0	7.2	5.4	-	4.0	11.3	7.7	-	8.8	7.7	10.0
C3	0.75 - 1.65 g/L	2.13	1.86	2.03	1.80	1.67	1.93	1.12	1.17	1.22	1.54	1.73	2.02	1.49	1.36	2.00
C4	0.14 - 0.54 g/L	0.45	0.43	0.45	0.30	0.28	0.40	0.27	0.30	0.32	0.24	0.30	0.36	0.10	0.15	0.21
C5	80.5 – 86.2 mg/L	76.9	75.2	93.4	71.3	80.4	94.7	86.5	76.1	78.9	103.5	94.8	92.9	-	-	-
C5a	8.8 – 22.3 µg/L	119.1	28.6	16.8	36.1	22.1	15.6	28.0	16.8	18.6	31.4	22.0	26.5	-	-	-
Terminal Complement Complex (TCC)	1.2-7.2 mg/L	17.3	6.5	3.3	13.1	3.2	8.6	10.3	3.8	5.3	11.3	5.5	12.9	12.4	2.1	7.6
Classical pathway haemolytic activity (CH50)	70-130 Haemolytic units (HU)	229.8	0	175.1	132.2	0	69.9	284.4	0	88.9	268.4	0	105.5	247.9	0	151.5

C-reactive protein	<5 mg/L	99	31	8	170	36	59	113	22	24	164	43	27	133	182	149
Ferritin	15-300 µg/L	666	599	354	350	266	169	3004	-	384	473	248	-	424	421	508
Lactate Dehydrogenase	125-200 U/L	478	329	469	500	533	370	571	-	287	306	241	-	313	315	326
Procalcitonin	<0.05 µg/L	0.14	0.08	0.05	0.57	0.27	0.20	3.27	3.09	1.01	0.08	0.05	-	1.32	0.48	0.66
Troponin I (high sensitivity)	0-34 ng/L (male)	23	13	12	-	-	-	89	-	46	-	-	-	9	20	44
	0-16 ng/L (female)	-	-	-	<2	<2	3	-	-	-	2	<2	-	-	-	-
Follow-up duration††	Days since admission (post LFG316)	81 (48)			50 (43)			63 (42)			49 (38)			20 (8)		
Current care level†††	1-6	1			1			3			1			6		
†- Steroids, total prednisolone equivalent dose given on CCU prior to administration of LFG316; in a comparator group of 28 clinically matched patients, steroid dose was 0.95g (sd +/- 0.27g).																
††-Correct at date of original submission, 12 th June 2020; censored at day 20 post admission for patient 5.																
†††-Care level at date of submission defined by six-point scale consisting of the following categories 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death.																

Figure 1.

